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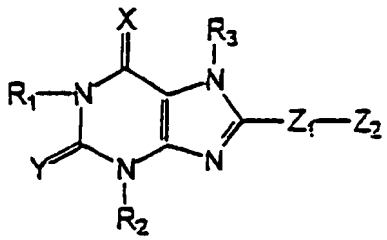
(54) Immunosuppressive effects of 8-substituted xanthine derivatives

(57) The invention relates to a novel use of 8 substituted xanthine derivatives for the manufacture of a medicament for the treatment of auto-immuno disorders.

The invention relates in particular to the use of a xanthine derivative of general formula (I):



wherein:

R_1, R_2 and R_3 are independently hydrogen, saturated or unsaturated aliphatic chains which may be straight or branched having 1 to 6 carbon atoms;
X and Y are independently oxygen or sulfur;
Z_1 is selected from the group comprising a thienyl; furanyl; cyclopentyl, phenyl or a substituted by Z_2 or unsubstituted phenyl; wherein Z_2 is selected from the group comprising phenyl; sulfonic acid; unsubstituted or N-substituted sulfonamide with substituents such as alkyl, aminoalkyl where the amino group may be substituted itself with lower alkyl groups bearing 1 to 4 carbon atoms; nitro; halogen substituted or unsubstituted amino group; aliphatic chain with 1 to 3 carbon atoms; halogenated aliphatic chain with 1 to 3 carbon atoms; aliphatic chain containing ether functions, acids, esters, amides, substituted or unsubstituted amines having 1 to 3 carbon atoms, nitro, sulfonamides or a combination of these functional groups with a maximum length of the chain of 12 atoms,

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of auto-immuno disorders.

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Description

[0001] The invention relates to a novel use of 8 substituted xanthine derivatives for the manufacture of a medicament for the treatment of auto-immuno disorders.

[0002] Methylxanthines, for example pentoxifylline (PTX) are known having immunosuppressive effects in vitro.

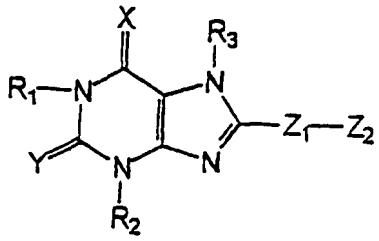
[0003] Several types of 8-substituted xanthine derivatives have been publicized, for example K.A. Jacobson et al. J. Med. Chem. **1993**, 36, 2639-2644; K.A. Jacobson et al. Biochem. Pharmacol. **1988**, 37, 3653-3661; K.A. Jacobson et al. J. Med. Chem. **1989**, 32, 1873-1879.

[0004] Recently (Lin Y. et al, Transplantation 63 (1997) it has been found that the co-medication of an immunosuppressive compound such as cyclosporine A (CyA) or FK506 or RPM (rapamycine) with a methyl xanthine derivative, in particular A802715 (7-propyl-1(5-hydroxy-5-methylhexyl)-3-methylxanthine) leads to a superadditive increase in the immunosuppressive action.

[0005] The immunosuppressive effect of cyclosporine A (CyA) is already known since 1972. However, due to its nephrotoxicity and several other side effects CyA has not been able to establish itself as the optimal and final drug of choice.

[0006] The present invention relates to a novel use of 8-substituted xanthine derivates and their pharmaceutical salts, possessing unexpectedly desirable pharmaceutical properties, i.c. are immunosupressive agents.

[0007] The invention demonstrates a novel use of xanthine derivatives of the formula (I):



wherein:

R_1, R_2 and R_3 are independently hydrogen, saturated or unsaturated aliphatic chains which may be straight or branched having 1 to 6 carbon atoms;
X and Y are independently oxygen or sulfur;
Z_1 is selected from the group comprising a thienyl; furanyl; cyclopentyl or a substituted by Z_2 or unsubstituted phenyl; wherein Z_2 is selected from the group comprising phenyl; sulfonic acid; unsubstituted or N-substituted sulfonamide with substituents such as alkyl, aminoalkyl where the amino group may be substituted itself with lower alkyl groups bearing 1 to 4 carbon atoms; nitro; substituted or unsubstituted amino group; aliphatic chain with 1 to 3 carbon atoms; halogenated aliphatic chain with 1 to 3 carbon atoms; aliphatic chain containing ether functions, acids, esters, amides, substituted or unsubstituted amines having 1 to 3 carbon atoms, nitro, sulfonamides or a combination of these functional groups with a maximum length of the chain of 12 atoms,
or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of auto-immuno disorders.

[0008] The invention further relates to a combination preparation, containing 1) cyclosporin A or FK506 or rapamycin, 2) at least one 8-substituted xanthine derivative of formula (I), and optionally a pharmaceutical excipient, for simultaneous, separate or sequential use in (auto)immune disorders.

[0009] Hereunder the effects of the 8-substituted xanthine derivatives on the lymphocyte activation are elucidated and are compared with non-substituted xanthine derivatives (see table I, compound 1,2,3,4,5,22,23,24,25,26, and 67,68,69,70,71).

[0010] Table I summarizes the tested compounds. These xanthine derivatives were obtained as follows:

Compound number 8, 10, 12, 14, 21, 36, 37, 38, 47, 48, 50, 51, 79, 83
K.A. Jacobson et al. J. Med. Chem. **1993**, 36, 2639-2644;

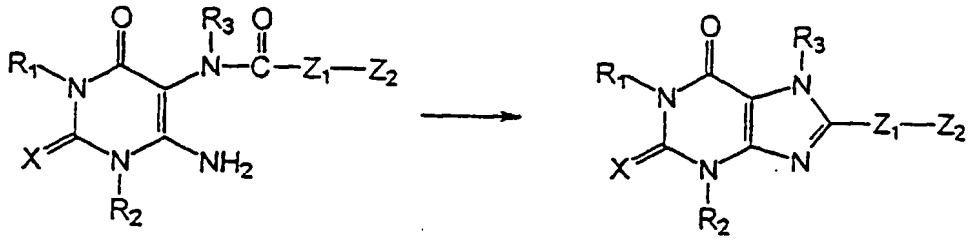
9, 11, 13, 30, 31, 39, 40, 41, 42, 43, 125
K.A. Jacobson et al. Biochem. Pharmacol. **1988**, 37, 3653-3661;

15, 17, 18, 28, 29, 33, 34, 35, 44, 45, 46, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 78, 80, 81
K.A. Jacobson et al. J. Med. Chem. **1989**, 32, 1873-1879;

[0011] Compoundnumbers **1, 2, 3, 4, 5, 22, 23, 24, 67, 68, 82, 112, 113, 114, 116, 117, 118, 119** (table I and II) were obtained by the following procedure for the alkylation of xanthine derivatives.

[0012] 0,01 mol of a xanthine derivative (**1a, 2a, 3a, 4a, 5a, 67a, 68a, 82a, 112a, 113a (114a), 116a (117a), 118a (119a)**). (The origin of these compounds is as follows: **1a** Theobromin, commercially available FLUKA AG; **2a** W. Traube, Ber. Deut. Chem. Ges. **33**, 3035 (1900); **3a** G. Elion, J. Org. Chem. **27**, 2478 (1962); **4a** W. Hutzenlaub, W. Pfleiderer, Liebigs Ann. Chem. **1979**, 1847; **5a** Xanthin, commercially available FLUKA AG; **67a** W. Hutzenlaub, W. Pfleiderer, Liebigs Ann. Chem. **1979**, 1847; **68a** P.G. Kjellin, C.G.A. Persson, Eur. Pat. Appl. 10 531; C.A. 94, P 15773 u; **82a** K.A. Jacobson, D. Shi, C. Gallo-Rodriguez, M. Manning, C. Müller, J.W. Daly, J.L. Neumeyer, L. Kiriasis, W. Pleiderer, J. Med. Chem. **36**, 2639 (1993); **112a** H. Goldner, G. Dietz, E. Carstens, Liebigs Ann. Chem. **691**, 142 (1966); **113a** M.T. Shamim, D. Ukena, W.L. Padgett, J.W. Daly, J. Med. Chem. **32**, 1231 (1989)] (see table II) were suspended or dissolved in DMF (60 ml) at room temperature and then under stirring K_2CO_3 (6 g per N-H function) and the alkylating agent (methyl iodide, ally iodide, propargyl bromide, n-propyl iodide, benzyl bromide, 2-chlorobenzyl bromide, 4-bromobutanoic acid, 5-bromopentanoic acid, ethyl 4-bromobutanoate) (0.015 mci per N-H) function added. The mixture was stirred at room temperature for 15 h, then the insoluble inorganic salts filtered off by suction and the filtrate evaporated in vacuum at 50°C to a syrup. The residue was treated with H_2O forming a colorless solid. The precipitate was collected and purified by recrystallization from H_2O/EtOH mixtures to give colorless crystals of **1, 2, 3, 4, 5, 67, 68, 82, 112, 113, 114, 116, 117, 118, 119**.

[0013] Compound numbers **16, 52, 53, 54, 69, 70, 71, 115, 116a (117a), 118a (119a)** (table I and III) were obtained by a procedure for the cyclization of 5-acylamino-6-aminouracils



[0014] The 5-acylamino-6-aminouracil (**16a, 52a, 53a, 54a, 69a, 70a, 71a, 115a, 116b, 118b**) (0.01 mol) was heated in a mixture of 2 NaOH (50 ml) and EtOH (10 ml) under reflux for 30 min. The hot solution was acidified by AcOH whereby a colorless precipitate separated. The solid was collected after cooling, dried and then purified by recrystallization from EtOH, DMF or by reprecipitation from alkaline solution by addition of AcOH.

General procedures for the synthesis of 5-acylamino-6-amino-uracils (16a, 52a, 53a, 54a, 69a, 70a, 71a, 115a, 116b, 118b) (table IV).

[0015]

a) 0.01 mol of the N-substituted 5,6-diaminouracil (**69b, 70b, 71b**) was heated in formic acid (20 ml) for 15 mm under reflux. The reaction mixture was evaporated to dryness and the residue recrystallized from water to give colorless crystals (**69a, 70a, 71a**). Yield: 75-90%.

b) 0.01 mol of the N-substituted 5,6-diaminouracil (**52b, 53b, 116c**) was treated with 0.012 mol of the appropiate acyl chloride (p-nitrobenzoyl chloride, p-biphenyl-4-carbonyl chloride, p-chlorbenzoyl chloride, p-aminobenzoyl chloride) in abs. pyridine (20 ml) with stirring at room temp. for 3 hours. It was evaporated, the residue treated with water and the resulting precipitate collected by suction. Recrystallization from EtOH/$H_2$0 yielded 70-90% of colorless crystals (**52a, 115a, 53a, 54a, 116b, 118b**).

c) 0.01 mol of the N-substituted 5,6-diaminouracil (**16b**) was suspended in EtOH (100 ml), then subsequently added 0.011 mol of the appropiate acid (p-sulfamoylbenzoic acid) and 0.012 mol of the condensing agent (dicyclohexylcarbodiimide), N-dimethylaminopropyl-N'-ethylcarbodiimide hydrochloride). The mixture stirred at room temp. for 2 hours, the precipitate filtered off and purified by recrystallization from EtOH to give colorless crystals

(**16a**). Yield: 80-90%.

General procedure for the synthesis of N-alkyl-5,6-diaminouracil (16b, 52b, 53b, 69b, 70b, 71b, 116c) (table V).

[0016]

a) 0.05 mol of 6-amino-3-methyl-1-neopentyluracil (**69c**), 6-amino-1,3-dimethyluracil (**52c**), 6-amino-1,3-di-n-propyluracil (**53c**), 6-amino-1-isopropyl-3-methyluracil (**71c**), 6-amino-1-n-propyluracil (**116d**) and 6-amino-1,3-di-n-propyl-2-thiouracil (**16c**), respectively, were suspended in a mixture of water (100 ml) and EtOH (20 ml) and heated to 50°C. Then $NaNO_2$ (4 g) was added and the stirring mixture acidified by dropwise addition of AcOH (5 ml) whereby intermediary solution with strong coloration takes place. A red to violet coloured precipitate consisting of the corresponding 5-nitroso derivative was formed. The solid was collected after cooling (85-90%) and used directly for reduction to the anticipated N-alkyl-5,6-diaminouracil (**69b, 52b, 53b, 71b, 116c, 16b**). 0.05 mol of the 6-amino-N-alkyl-5-nitrosouracil derivative was added under stirring to a warm solution (50°C) of ammonium sulfide (25 ml) and then the temperature raised to 80°C for 15 mm. On cooling the resulting precipitate was filtered off by suction, washed with water and little MeOH and then dried in a vacuum desiccator to give 75-90% of colorless to yellowish crystals.

b) **6-Amino-5-methylamino-1-neopentyluracil** (**70b**). 6-Amino-1-neopentyluracil (**70c**) (3.94 g, 0.02 mol) was treated in AcOH (40 ml) at 80°C in presence of NaOAc x 3 H_2O (2.6 g, 0.02 mol) with bromine (3.2 g, 0.02 mol) by dropwise addition. After 2 hours was cooled, the precipitate (75%) collected, washed with water and dried. 6-Amino-5-bromo-1-neopentyluracil (2.76 g, 0.01 mol) was then stirred in a 40% aqueous methylamine solution (80 ml) at room temp. for 2 days. The mixture was evaporated to half its volume and the precipitate collected. Washing with water and drying in a desiccator yielded 2.05 g (90%) of **70b**. M.P. 217-220°C.

Syntheses of N-alkyl-6-aminouracils.

[0017] **6-Amino-1-neopentyluracil (70c).** N-neopentylurea (13.0 g, 0.1 mol) and ethyl cyanoacetate (10 ml) were heated in 4N NaOEt (100 ml) for 4 hours under reflux. The reaction mixture was evaporated to dryness, the residue treated with water (100 ml) and then acidified with AcOH to pH 4-5 to form a colorless precipitate. Yield: 11.2 g (59%).

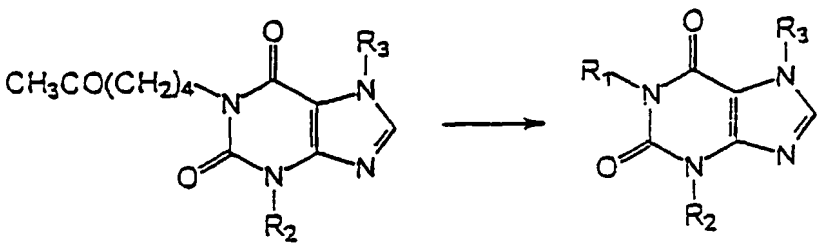
[0018] **6-Amino-3-methyl-1-neopentyluracil (69c).** 6-Amino-1-neopentyluracil (**90c**) (5.9 g, 0.03 mol) were dissolved in 1 N NaOH (50 ml) and then unrder vigorous stirring dimethylsulfate (3.9 ml, 0.033 mol) dropwise added at room temp. A precipitate separated and was collected after 2 hours. After washing with water and drying in a vacuum desiccator resulted 5.76 g (91%) of colorless crystals.

[0019] **6-Amino-3-methyl-1-n-isopropyluracil (71c).** 6-Amino-1-isopropyluracil (16.9 g, 0.1 mol) were dissolved in 1 N NaOH (120 ml) and then at room temp. dimethylsulfate (12 ml, 0.12 mol) dropwise added with vigorous stirring. After 1 hour the precipitate was collected, washed with water and dried at 50°C in high vacuum to give 15.1 g (82%) of chromatographically pure, colorless crystals.

[0020] **6-Amino-1-n-propyluracil (116d).** N-n-propylurea (20.4 g, 0.2 mol) and ethyl cyanoacetate (20 ml) were heated in 3 N NaOMe (200 ml) for 3 hours under reflux. The reaction mixture was evaporated, the residue treated with 100 ml of water and acidified with AcOH to pH 4 to give 23.7 g (70%) of colorless crystals.

[0021] **6-Amino-1,3-di-n-propyl-2-thiouracil (16c).** To a mixture of cyanoacetic acid (10 g) and acetic anhydride (50 ml) was added N,N'-di-n-propylthiourea (16 g, 0.01 mol) and stirred at 60°C for 4 hours. It was evaporated to dryness, the residue treated with 30% NaOH (100 ml) for 30 min, then diluted with water (100 ml) and the precipitate collected. Recrystallization from EtOH/water gave 18 g (79%) of yellowish crystals. The same procedure and started from N,N'-dimethylurea or N,N'-di-n-propylurea yielded 6-amino-1,3-dimethyluracil (**52c**) and 6-amino-1,3-di-n-propyluracil (**53c**) respectively as colorless crystals.

[0022] Compoundnumbers 25 and 26 (table I and table III) were obtained by a general procedure for the sythesis of 1-(5-hydroxyhexyl)xanthines.



[0023] 3,7-Dialkyl-1-(hexan-5-onyl)xanthine (2 mmol) was dissolved in MeOH (15 ml) and then created under stirring with $NaBH_4$ (0.1 g) overnight. The mixture was evaporated to dryness, the residue diluted with H_2O, then extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, filtered and the filtrate again evaporated to give a chromatographically pure solid. The solid was stirred in n-hexane for 1 h, then filtered by suction and dried in a vacuum destillator to give a colorless crystal powder.

[0024] Compounds **19, 20** and **66** were obtained by methylation of **55, 57** and **64** respectively. 0.01 Mol of the purine **55, 57** and **64,** respectively, was dissolved in DMF (120 ml) by warming. After cooling to room temperature K_2CO_3 (7 g) and methyl iodide (2 ml) were added and then the mixture stirred for 3 hours. The solution was then diluted with H_2O (150 ml) and after cooling the precipitate collected, washed with water and dried. Recrystallization from EtOH/H_2O gave colorless crystals in 75-90% yield. M.p. 198°C (**19**), 298°C (**20**) and 197°C (**66**).

[0025] The synthesis of compound **32** is based on compound **33,** which is described in literature [K.A. Jacobson, K.L. Kirk, W.L. Padgett, J.W. Daly, J. Med. Chem. **1985**, 28, 1334]. Compound **33** (2.14 g, 0.005 mol) was suspended in abs. pyridine (50 ml) and then under stirring chlorosulfonic acid (4 ml) added dropwise. It was heated to 50°C with stirring for 12 hours. The reaction mixture was evaporated in vacuum, coevaporated twice with EtOH and the residue recrystallized from H_2O/EtOH to give 1.95 g (77%) of **32** of a colorless crystal powder. M.p. 245°c.

Materials and methods

[0026] Various models may be used for testing an immunosuppressive effect. In vivo, for example, different transplantation models are available. They are strongly influenced by different immunogenicities, depending on the donor and recipient species used and depending on the nature of the transplanted organ. The survival time of transplanted organs can thus be used to measure the suppression of the immune response. In vitro, there exist also various models. The most used are lymphocyte activation tests. Usually activation is measured via lymphocyte proliferation. Inhibition of proliferation thus always means immunosuppression under the experimental conditions applied. There exist different stimuli for lymphocyte activation:

- coculture of lymphocytes of different species (MLR = mixed lymphocyte reaction): lymphocytes expressing different minor and major antigens of the HLA-DR type (= allogens) activate each other non-specifically.
- CD3 assay: here there is an activation of the T-lymphocytes via an exogenously added antibody (OKT3). This antibody reacts against the CD3 molecule located on the lymphocyte membrane. This molecule has a costimulatory function. The interaction anti-CD3 (= OKT3)-CD3 results in T-cell activation which proceeds via the Ca^2+/calmodulin/cacineurin system and can be inhibited by CyA.
- CD28 assay: here specific activation of the T-lymphocyte goes also via an exogenously added antibody against the CD28 molecule. This molecule is also located on the lymphocyte membrane, and delivers strong costimulatory signals. This activation is Ca^2+-independent and thus cannot be inhibited by CyA.
- IL-2R assay: here activation of the lymphocyte occurs via the exogenously added cytokine IL-2 which binds to the IL-2 receptor (IL-2R) that is located on the lymphocyte membrane of prestimulated T cells. This activation is also Ca^2+/cAMP-independent and cannot be inhibited by CyA.

Reagents

[0027] All derivatives were dissolved in 0.5 ml DMSO and further diluted in culture medium before use in in vitro experiments. The culture medium consisted of RPMI-1640 + 10% FCS.

Mixed Lymphocyte Reaction

[0028] Peripheral blood mononuclear cells (PBMC) were isolated from heparinized peripheral blood by density gradient centrifugation over Lymphoprep (Nycomed, Maorstua, Norway). Allogeneic PBMC or EBV-transformed human B cells [RPMI1788 (ATCC name CCL156)] which strongly express B7-1 and B7-2 were used as stimulator cells after irradiation with 30 Gy. MLR was performed in triplicate wells. After 5 days incubation at 37°C, 1 μCi [^{3}H]-thymidine was added to each cup. After a further 16 hours incubation, cells were harvested and counted in a β-counter.

[0029] The percent suppression of proliferation by drugs was counted using the formula:

$$\text{Per cent inhibition} = \frac{\text{(cpm+drugs) - cpm Cult.Med.)}}{\text{(cpm-drugs) - cpm Cult.Med.)}} \times 100$$

T cell purification

[0030] T cells were purified by removing non-T cells. Briefly, monocytes were removed by cold agglutination. The resulting lymphoid cells were further purified by a cell enrichment immunocolumn [Cellect Human T (Biotex, Edmonton, Alberta, Canada)] by a process of negative selection. More than 95% of the B cells were removed with this procedure. After depletion, the resulting T cell preparation was highly purified explaining these cells could not be activated by PHA or rIL-2 alone at concentrations capable of stimulating RBMC prior to deletion.

Measurements of T cell proliferations induced by anti-CD3 mAb + PMA or anti-CD28 mAb + PMA

[0031] Highly purified T cells (10^6/ml) were stimulated by immobilized anti-CD3 or anti-CD28 mAb in the presence of PMA. Anti-CD3 mAb (CLB-CD3; CLB, Amsterdam, The Netherlands) were fixed on the 96-microwell plates by incubating the wells with 50 μl of mAb solution (CLB-CD28; CLB, Amsterdam, The Netherlands) 50 μl (1/650 dilution in culture medium) was added directly to the wells. Further, 20 μl PMA (Sigma, St. Louis, MO, USA) solution (final concentration: 0.5 ng/ml) was added. Subsequently, 20 μl of immunosuppressants were added by serial dilution in triplicate wells. Finally 100 μl of the T cell suspension (10^6/ml) was added. After 48-hour incubation at 37°C in 5% CO_2 20 μl BrdU (100 μM solution) (Cell Proliferation Elisa, Boehringer-Mannheim Belgium) was added to each well. After a further overnight incubation the T cell proliferation was measured using a colorimetric immunoassay for qualification of cell proliferation based on measurements of the incorporation of BrdU during DNA synthesis. The optical density (OD) was measured by a Behring EL311 place reader at 450 nm (reference wavelength: 690 nm). The percent suppression of proliferation by drugs was counted using the formula:

$$\text{Per cent inhibition} = \frac{\text{(OD+drugs) - (OD Cult. Med.)}}{\text{(OD-drugs) - (OD Cult. Med.)}} \times 100$$

In vitro immunosuppressive effect of Xanthine Derivatives as measured with the MLR and with tests involving polyclonal T cell proliferation induced by anti-CD3 mAb + PMA or anti-CD28 mAb + PMA (table VI)

[0032]

- In the tabe VI column II shows the IC50 values of the various substances in the MLR. The IC50 value represents the lowest concentration of the substances that resulted in a 50% suppression of the MLR.
- Column III shows the IC50 value of the various substances for the anti-CD3 mAb + PMA pathway and row IV the IC50 values of the various substances for the anti-CD28 mAb + PMA pathway.
- As a comparison the values of other immunosuppressants: CsA, FK506, Rapamycin, Leflunomide and Mycophenolic acid are given as well.

[0033] Whole Blood Assay (WBA): WBA is a lymphoproliferation assay performed in vitro but using lymphocytes present in whole blood, taken from animals that were previously given test substances in vivo. Hence it reflects the in vivo effect of substances as assessed with an in vitro read-out assay.

[0034] Rats: inbred, male 6- to 8-weeks old R/A rats weighing ± 200 g were used as recipients.

[0035] Drug administration: Xanthine derivatives were dissolved in DMSO and further diluted with PBS. Products were given orally in different concentrations 2 times a day for 2 days. To perform the experiments, 6-8 hours after the last administration 1 ml of blood is taken by heart puncture after ether anesthesia and anticoagulated with 100 U/ml of

preservative free heparine.

[0036] Whole Blood Assay: This assay was performed as we described previously [Use of the Methylxanthine Derivatives A802715 in Transplantation Immunology. II In vitro Experiments. (Yuan Lin, et al., Transplantation **1997**, 63, No. 12, 1734-1738)].

[0037] Heparinized whole blood was diluted (1:25) with complete RPMI medium and stimulated with 15 µg/ml of concanavalin A (Con A) in triplicate wells in 96-well microtiter plates at 37°C and 5% CO_2. After 96-h culture, proliferation was determined by measuring the incorporation (cpm) of [^{3}H]-thymidine.

[0038] The Con A induced proliferation of lymphocytes taken from rats receiving the test substances (exp) was compared with that from rats receiving only the solvent (con). The percent suppression was calculated as follows:

$$\%\ \text{sup pression}: 100-\left[\frac{\text{cpm exp}}{\text{cpm con}} x100\right]$$

Results			
Nr	% suppression	Administration of drugs	Blood taken after:
11	33	40mg/kg/d 2x/d 2d	8 h
14	86	40mg/kg/d 2x/d 2d	8 h

[0039] First, most of the substances according to the invention have a clear suppressive effect in the MLR (mixed lymphocyte reaction). The MLR is considered as an in vitro analogue of the transplant rejection as it is based on the recognition of allogeneic MHC (major histocompatibility antigens) on the stimulator leucotyes, by responding lymphocytes. Various established immunosuppressive drugs are known to suppress the MLR, and were also shown in this description. Further, the 8-substitutd xanthine derivatives are more effective than the non-substituted.

[0040] From these data it can be deduced that the 8-substituted xanthine derivatives may be effective in clinical situations where other immunosuppressants are active as well.

[0041] These include the prevention and/or treatment of organ transplant rejection, the prevention and/or treatment of both rejection and the occurrence of graft-versus-host-disease after BM transplantation; the prevention and/or treatment of autoimmune diseases including diabetes mellitus, multiple sclerosis, glomerulonephritis, rheumatoid arthritis, proriasis systemic diseases such as vasculitis; scleroderma, polymyositis, autoimmune endocrine disorders (thyroiditis), ocular diseases (uveitis), inflammatory bowel diseases (Crohn's disease, colitis uclerosa), autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis) autoimmune pneumonitis and auto-immune carditis.

[0042] Whereas cyclosporine A and FK506 are only active in the anti-CD3 + PMA test, the 8-substituted xanthine derivatives according to the invention were active, not only in the anti-CD3 + PMA but also in the anti-CD28 + PMA test. It has been shown that the latter is Ca-calmodulin resistant, and resistant to CsA and FK506. The anti-CD28 + PMA pathway has also been called the cosignal pathway and is important to induce energy and even tolerance in T cells. Moreover, representative compounds have been found to be active in a whole blood assay.

[0043] Under the term "organ" in the description is understood all organs or parts of organs (even several) in mammals, in particular humans, for example kidney, heart, skin, liver, muscle, cornea, bone, bone marrow, lung, pancreas, intestine or stomach.

[0044] After organ transplantation, rejection of the transplanted organ by the recipient occurs (host-versus-graft reaction). After bone marrow transplantation, also rejection of the host by the grafted cell may occur (graft-versus-host reaction). Rejection reactions mean all reactions of the recipient body or of the transplanted organ which in the end lead to cell or tissue death in the transplanted organ or adversely affect the functional ability and viability of the transplanted organ or adversely affect the functional ability and viability of the transplanted organ or the recipient. In particular, this means acute and chronic rejection reactions.

[0045] Auto-immune disorders include, inter alia, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, pemphigus, atopic dermatitis, myositis, multiple sclerosis, nephrotic syndrome (in particular glomerulonephritis), ulcerative colitis or juvenile diabetes.

[0046] The invention further relates to the use of cyclosporin A or FK506 or Rapamycine and at least one 8-substituted xanthine according to the invention for the production of a pharmaceutical for inhibiting the replication of viruses such as picorna-, toga-, bunya-, orthomyxo-, paramyxo-, rhabdo-, retro-, arena-, hepatitis B-, hepatitis C-, hepatitis D-, adeno-, vaccinia-, papilloma-, herpes-, varicella-zoster-virus or human immunodeficiency virus (HIV); or for treating of

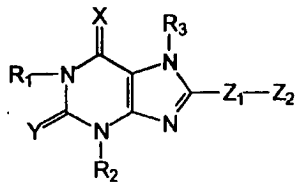
cancer such as lung cancers, leukaemia, ovarian cancers, sarcoma, Kaposi's sarcoma, meningioma, colon cancers, lymp node tumors, glioblastoma multiforme, prostate cancers or skin carcinoses.

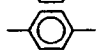
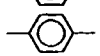
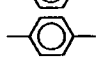
[0047] The invention further relates to the use of cyclosporin A or FK506 or rapamycin and at least one xanthine of the general formula for the production of a pharmaceutical for the treatment of human after organ transplantation or of (auto)immune disorders.

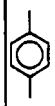
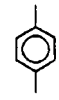
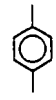
[0048] Hence, the advantage to associate xanthine with other immunosuppressants may be that, first, the therapeutic spectrum of action of the individual components is quantitatively and qualitatively broadened. Secondly that it allows, by means of a dose reduction without reduced efficacy but with increased safety, that the treatment of immune disorders which were hitherto no indication for immunosuppressive therapy as a result of side effects may be considered. At the same time, the therapy costs can be decreased to an appreciable extent.

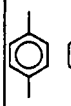
[0049] The prefered compounds according to the invention are the xantine derivates bearing on the 8-position a substituted or unsubstituted phenyl.

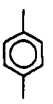
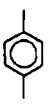
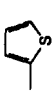
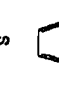
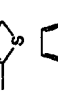
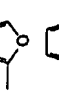
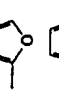
Table 1



Compound n°	R_1	R_2	R_3	X	Y	Z_1	Z_2
1	$CH_2C\equiv CH$	CH_3	CH_3	O	O	H	-
2	$CH_2C\equiv CH$	CH_3	$CH_2C\equiv CH$	O	O	H	-
3	CH_3	$CH_2C\equiv CH$	$CH_2C\equiv CH$	O	O	H	-
4	$CH_2C\equiv CH$	$CH_2C\equiv CH$	CH_3	O	O	H	-
5	$CH_2C\equiv CH$	$CH_2C\equiv CH$	$CH_2C\equiv CH$	O	O	H	-
8	CH_2-CH=CH_2	CH_3	CH_2-CH=CH_2	O	O		-
9	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$-SO_2NHCH_2CH_2NMe_2$
10	CH_3	CH_3	CH_3	O	O		CF_3
11	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$-SO_2NH(CH_2)_3NEt_2$
12	CH_2-CH=CH_2	CH_3	CH_3	O	O		CF_3
13	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$-OCH_2CONH(CH_2)_2NEt_2$
14	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$CH_2CH=CH_2$	O	O		CF_3
15	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		-

Compound n°	R_1	R_2	R_3	X	Y	Z_1	Z_2
16	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		SO_2NH_2
17	CH_3	CH_3	H	S	O		-
18/	CH_3	CH_3	H	S	S		-
19	CH_3	CH_3	CH_3	O	O		-
20	CH_3	CH_3	CH_3	O	S		-
21	$CH_2CH=CH_2$	CH_3	CH_3	O	O		SO_3Na
22	$-(CH_2)_4COOH$	CH_3	CH_3	O	O	H	-
23	$-(CH_2)_3COOH$	CH_3	CH_3	O	O	H	-
24	$-(CH_2)_3COOEt$	CH_3	CH_3	O	O	H	-
25	$-(CH_2)_4CHOH-CH_3$	CH_3	CH_3	O	O	H	-
26	$-(CH_2)_4CHOH-CH_3$	CH_3	$CH_2CH_2CH_3$	O	O	H	-
28	$-CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		$-OCH_2COOH$
29	$-CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		$-OCH_2COOEt$
30	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		OCH_2COOMe
31	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$OCH_2CONH(CH_2)_3NHCOCH_3$
32	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$OCH_2CONH(CH_2)_2NHSO_3H$

Compound n°	R_1	R_2	R_3	X	Y	Z_1	Z_2
33	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$OCH_2CONH(CH_2)_2$-NH_2
34	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$OCH_2CONH(CH_2)_2NMe_2$
35	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		$OCH_2CONH(CH_2)_2NH_2$
36	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$-SO_2NH_2$
37	H	CH_3	CH_3	O	O		SO_2NH_2
38	H	CH_3	CH_3	O	O		SO_2H
39	CH_3	CH_3	H	O	O		$SO_2NH(CH_2)_2NH_2$
40	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		$SO_2NH(CH_2)_3NMe_2$
41	CH_3	CH_3	H	O	O		$SO_2NH(CH_2)_2NMe_2$
42	CH_3	CH_3	H	O	O		$SO_2NH(CH_2)_3NMe_2$
43	CH_3	CH_3	H	O	O		$SO_2NH(CH_2)_3NEt_2$
44	CH_3	CH_3	H	O	S		-
45	CH_3	CH_3	H	S	O		-
46	CH_2CH_3	CH_2CH_3	H	S	O		-

Compound n°	R	R_2	R_3	X	Y	Z_1	Z_2
47	H	CH_3	CH_3	O	O		-
48	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		CF_3
50	$CH_2CH=CH_2$	CH_3	CH_3	O	O		-
51	CH_3	CH_3	H	O	O		CF_3
52	CH_3	CH_3	H	O	O		NO_2
53	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		NO_2
54	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		NH_2
55	CH_3	CH_3	H	O	O		-
56	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		-
57	CH_3	CH_3	H	O	S		-
58	CH_3	CH_3	H	O	O		-
59	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		-
60	CH_3	CH_3	H	O	S		-

Compound n°	R_1	R_2	R_3	X	Y	Z_1	Z_2
61	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		-
62	CH_3	CH_3	H	O	O		-
63	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		-
64	CH_3	CH_3	H	O	S		-
65	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		-
66	CH_3	CH_3	CH_3	O	S		-
67	CH_3	$CH_2C{\equiv}CH$	CH_3	O	O	H	-
68	CH_3	$CH_2C(CH_3)_3$	CH_3	O	O	H	-
69	CH_3	$CH_2\text{-}C(CH_3)_3$	H	O	O	H	-
70	H	$CH_2C(CH_3)_3$	CH_3	O	O	H	-
71	CH_3	-$CH(CH_3)_2$	H	O	O	H	-
78	CH_3	CH_3	H	O	O		-
79	CH_3	CH_3	CH_3	O	O		-
80	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	O		-
81	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	O	S		-
82	CH_3	CH_3	$CH_2CH{=}CH_2$	O	O		CF_3

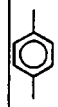
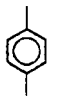
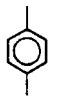
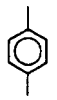
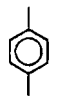
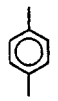
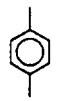
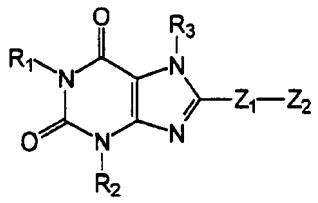
Compound n°	R_1	R_2	R_3	X	Y	Z_1	Z_2
83	H	CH_3	CH_3	O	O		CF_3
112	CH_3	CH_3	$CH_2CH_2CH_3$	O	O		-
113	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	O	O		-
114	CH_2-CH=CH_2	$-CH_2CH_2CH_3$	CH_2-CH=CH_2	O	O		-
115	CH_3	CH_3	H	O	O		
116	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	O	O		
117	CH_2-CH=CH_2	$CH_2CH_2CH_3$	CH_2-CH=CH_2	O	O		
118	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	O	O		Cl
119	CH_2-CH=CH_2	$CH_2CH_2CH_3$	CH_2-CH=CH_2	O	O		Cl
125	CH_3	CH_3	H	O	O		$-SO_2NH_2$

Table II



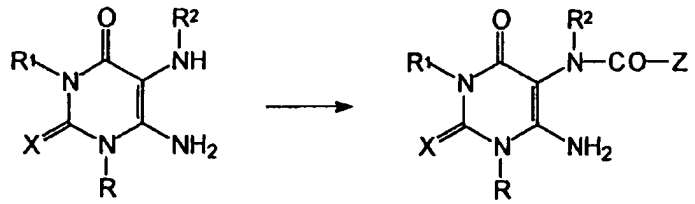
	R_1	R_2	R_3	Z_1	Z_2	Mp
1a	H	CH_3	CH_3	H	-	
1	$HC\equiv C-CH_2$	CH_3	CH_3	H	-	204°
2a	H	CH_3	H	H	-	
2	$HC\equiv C-CH_2$	CH_3	$HC\equiv C-CH_2$	H	-	177°
3a	CH_3	H	H	H	-	
3	CH_3	$HC\equiv C-CH_2$	$HC\equiv C-CH_2$	H	-	174°
4a	H	H	CH_3	H	-	
4	$HC\equiv C-CH_2$	$HC\equiv C-CH_2$	CH_3	H	-	172°
5a	H	H	H	H	-	
5	$HC\equiv C-CH_2$	$HC\equiv C-CH_2$	$HC\equiv C-CH_2$	H	-	155°
22	$HOOC(CH_2)_4$	CH_3	CH_3	H	-	195°
23	$HOOC(CH_2)_3$	CH_3	CH_3	H	-	208-210°
24	$EtOOC(CH_2)_3$	CH_3	CH_3	H	-	86-88°
67a	CH_3	H	CH_3	H	-	
67	CH_3	$HC\equiv C-CH_2$	CH_3	H	-	
68a	H	$CH_2C(CH_3)_3$	H	H	-	
68	CH_3	$CH_2C(CH_3)_3$	CH_3	H	-	158°
82a	CH_3	CH_3	H	$-C_6H_4-$	p-CF_3	
82	CH_3	CH_3	$CH_2=CHCH_2$	$-C_6H_4-$	p-CF_3	116-118°
112a	CH_3	CH_3	H	$-C_6H_5$	-	
112	CH_3	CH_3	$CH_3CH_2CH_2$	$-C_6H_5$	-	141°
113a	H	$CH_3CH_2CH_2$	H	$-C_6H_5$	-	
113	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$-C_6H_5$	-	123-125°
114a	H	$CH_3CH_2CH_2$	H	$-C_6H_5$	-	
114	$CH_2=CHCH_2$	$CH_3CH_2CH_2$	$CH_2=CHCH_2$	$-C_6H_5$	-	113-114°
116a	H	$CH_3CH_2CH_2$	H	$-C_6H_4$	p-C_6H_5	
116	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$-C_6H_4$	p-C_6H_5	116°

	R_1	R_2	R_3	Z_1	Z_2	Mp
117a	H	$CH_3CH_2CH_2$	H	$-C_6H_4$	p-C_6H_5	
117	CH_2=$CHCH_2$	$CH_3CH_2CH_2$	CH_2=$CHCH_2$	$-C_6H_4$	p-C_6H_5	104-106°
118a	H	$CH_3CH_2CH_2$	H	$-C_6H_4$	p-Cl	
118	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$-C_6H_4$	p-Cl	71-74°
119a	H	$CH_3CH_2CH_2$	H	$-C_6H_4$	p-Cl	
119	CH_2=$CHCH_2$	$CH_3CH_2CH_2$	CH_2=$CHCH_2$	$-C_6H_4$	p-Cl	89-91°

Table III

	R_1	R_2	R_3	X	Z_1	Z_2	Mp
16	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	H	S	$-C_6H_4$	p-SO_2NH_2	> 300°
25	$CH_3CHOH(CH_2)_4$	CH_3	CH_3				118-120°
26	$CH_3CHOH(CH_2)_4$	CH_3	$CH_3CH_2CH_2$				72-74°
52	CH_3	CH_3	H	O	$-C_6H_4$	p-NO_2	275°
53	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	H	O	$-C_6H_4$	p-NO_2	> 270°
54	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	H	O	$-C_6H_4$	p-NO_2	> 300°
69	CH_3	$CH_2C(CH_3)_3$	H	O	H	-	234°
70	H	$CH_2C(CH_3)_3$	CH_3	O	H	-	248°
71	CH_3	$CH(CH_3)_2$	H	O	H	-	230°
115	CH_3	CH_3	H	O	$-C_6H_4-$	p-C_6H_5	> 300°

Table IV



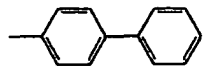
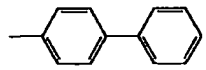
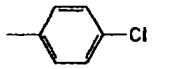
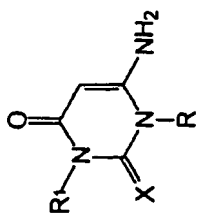
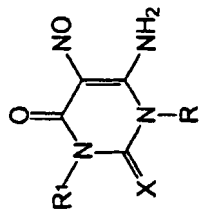
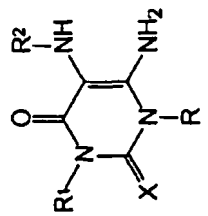
	R	R^1	R^2	X		R	R^1	R^2	X	Z	M.p.
16b	n-Pr	n-Pr	H	S	16a	n-Pr	n-Pr	H	S	p-C_6H_4-SO_2NH_2	268-270°
52b	Me	Me	H	O	52a	Me	Me	H	O	p-C_6H_4-NO_2	
53b	n-Pr	n-Pr	H	O	53a	n-Pr	n-Pr	H	O	p-C_6H_4-NO_2	>250° dec
69b	CH_2CMe_3	Me	H	O	54a	n-Pr	n-Pr	H	O	p-C_6H_4-NH_2	
71b	$CHMe_2$	Me	H	O	69a	CH_2CMe_3	Me	H	O	H	235-237°
70b	CH_2CMe_3	H	Me	O	71a	$CHMe_2$	CH_3	H	O	H	
116c	n-Pr	H	H	O	70a	CH_2CMe_3	H	CH_3	O	H	267-270°
					116b	n-Pr	H	H	O		288-290°
					115a	Me	Me	H	O		180°
					118b	n-Pr	H	H	O		269-272°

Table V







	R	R¹	X		R	R¹	R²	X	M.p.
70c	CH_2CMe_3	H	O	70b	CH_2CMe_3	H	Me	O	>237° dec
69c	CH_2CMe_3	Me	O	69b	CH_2CMe_3	Me	H	O	108-110°
16c	n-Pr	n-Pr	S	16b	n-Pr	n-Pr	H	S	110-113°
52c	Me	Me	O	52b	Me	Me	H	O	
53c	n-Pr	n-Pr	O	53b	n-Pr	n-Pr	H	O	
71c	$CHMe_2$	Me	O	71b	$CHMe_2$	Me	H	O	
116d	n-Pr	H	O	116c	n-Pr	H	H	O	

Table VI

Nr	IC50 in μM			Nr	IC50 in μM		
	Xanthine derivatives				Xanthine derivatives		
	MLR	aCD3	aCD28		MLR	aCD3	aCD28
1	> 200	150	> 200	25	> 200	140	160
2	> 200	> 200	100	26	100	100	100
3	150	150	100	28	120	150	75
4	> 200	90	> 200	29	> 200	150	130
5	> 200	50	> 200	30	> 200	140	100
8	30	35	80	31	200	120	80
9	25	40	50	32	70	90	110
10	50	20	30	33	160	45	35
11	25	40	55	34	105	45	60
12	30	90	80	35	50	50	70
13	ND	35	40	36	> 200	45	40
14	15	40	35	37	> 200	150	150
15	ND	> 200	170	38	> 200	120	120
16	ND	25	20	39	100	120	140
17	80	30	40	40	25	60	70
18	120	75	40	41	120	80	90
19	ND	50	80	42	170	130	130
20	ND	170	50	43	115	120	90
21	ND	180	80	44	120	170	120
22	> 200	> 200	> 200	45	165	25	25
23	> 200	> 200	> 200	46	> 200	25	20
24	> 200	170	150				

Nr	IC50 in µM		
	Xanthine derivatives		
	MLR	aCD3	aCD28
47	200	140	140
48	180	160	150
49	ND	ND	ND
50	180	200	120
51	200	200	200
52	80	180	90
53	110	160	110
54	120	130	130
55	> 200	200	120
56	> 200	170	100
57	> 200	> 200	180
58	> 200	160	170
59	15	155	135
60	> 200	200	190
61	100	170	110
62	> 200	> 200	190
63	> 200	135	100
64	> 200	> 200	> 200
65	> 200	135	75
66	> 200	170	170
67	> 200	> 200	200
68	75	130	120
69	120	110	45
70	> 200	180	140
71	160		

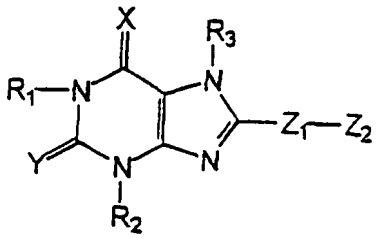
Nr	IC50 in µM		
	Xanthine derivatives		
	MLR	aCD3	aCD28
77	130		
78	> 200	> 200	> 200
79	75	100	130
80	160	120	65
81	> 200	180	110
82	25	80	80
83	> 200	> 200	150
112	20	45	40
113	20	110	90
114	15	85	70
115	110	> 200	160
116	160	45	40
117	15	30	30
118	15	15	20
119	15	50	30
125	160	150	90
132	> 200	> 200	> 200

I.S.	IC50		
	Immunosuppressant		
	MLR	aCD3	aCD28
CyA	20 nM	50 nM	N.S.
FK506	1 nM	1 nM	N.S.
Rapamycin	1 nM	1 nM	1 nM
Leflunomide	25 μM	15 μM	20 μM
Mofetil	<0.5μM	50 nM	50 nM

N.S. = not suppressive even not in the highest concentration

Claims

1. Use of a xanthine derivative of general formula (I):



wherein:

R_1, R_2 and R_3 are independently hydrogen, saturated or unsaturated aliphatic chains which may be straight or branched having 1 to 6 carbon atoms;
X and Y are independently oxygen or sulfur;
Z_1 is selected from the group comprising a thienyl; furanyl; cyclopentyl, phenyl or a substituted by Z_2 or unsubstituted phenyl; wherein Z_2 is selected from the group comprising phenyl; sulfonic acid; unsubstituted or N-substituted sulfonamide with substituents such as alkyl, aminoalkyl where the amino group may be substituted itself with lower alkyl groups bearing 1 to 4 carbon atoms; nitro; halogen substituted or unsubstituted amino group; aliphatic chain with 1 to 3 carbon atoms; halogenated aliphatic chain with 1 to 3 carbon atoms; aliphatic chain containing ether functions, acids, esters, amides, substituted or unsubstituted amines having 1 to 3 carbon atoms, nitro, sulfonamides or a combination of these functional groups With a maximum length of the chain of 12 atoms,
or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of auto-

immuno disorders.

2. Use according to claim 1, wherein

R_1, R_2 and R_3 are independently hydrogen; saturated or unsaturated straight aliphatic chains having 1 to 3 carbon atoms; and
Z_1 is a substituted or unsubstituted phenyl.

3. Use according to claim 1 or 2, wherein the xanthine derivative is compound selected from the group comprising:

1,7-diallyl-3-methyl-8-fenylxanthine (8);
1,3-dipropyl-8-[4(dimethylamino(ethyl(amino(sulfonyl))))fenyl]xanthine (9);
1,3,7-trimethyl-8-(4-trifluoromethylfenyl)xanthine (10);
1,3-dipropyl-8-[4(diethylamino(propyl(amino(sulfonyl))))fenyl]xanthine (11);
1,3-dipropyl-2-thio-8-[4-((((N-2-aminoethyl)amino)carbonyl)methyl)oxy)fenyl]xanthine (35);
1,3-dipropyl-8-[4-dimethylamino(propyl(amino(sulfonyl))))fenyllxanthine (40);
1,3-dimethyl-7-propyl-8-fenylxanthine (112);
1,7-diallyl-3-propyl-8-(p-bifenyl)xanthine (117);
1,3,7-tripropyl-8-(4-chlorofenyl)xanthine (118);
1,7-diallyl-3-propyl-8-(4-chlorofenyl)xanthine (119).

4. Product containing a compound according to any of the preceding claims 1-3 and at least a compound selected from the group comprising cyclosporine A, FK506, Rapamycin, Leflunomide, Mofetil.

5. Use of a product according to claim 4, as a combined preparation for simultaneous separate or sequential use in the treatment of auto-immuno disorders.

6. Compound having the formula:

1-propynyl-3,7-dimethylxanthine (1);
1,7-dipropynyl-3-methylxanthine (2);
1-methyl-3,7-dipropynylxanthine (3);
1,3-dipropynyl-7-methylxanthine (4);
1,3,7-tripropynylxanthine (5);
1-(4-carboxybutyl)-3,7-dimethylxanthine (22);
1-(3-carboxypropyl)-3,7-dimethylxanthine (23);
1-(3-ethoxycarbonyl)propyl-3,7-dimethylxanthine (24);
1,7-dimethyl-3-propynylxanthine (67);
1,7-dimethyl-3-((tertbutyl)methyl)xanthine (68);
1,3-dimethyl-7-allyl-8-[(4-trifluoromethyl)fenyl]xanthine (82);
1,3-dimethyl-7-propyl-8-fenylxanthine (112);
1,3,7-tripropyl-8-fenylxanthine (113);
1,7-diallyl-3-propyl-8-fenylxanthine (114);
1,3,7-tripropyl-8-(p-bifenyl)xanthine (116);
1,7-diallyl-3-propyl-8-(p-bifenyl)xanthine (117);
1,3,7-tripropyl-8-(4-chlorofenyl)xanthine (118);
1,7-diallyl-3-propyl-8-(4-chlorofenyl)xanthine (119).

7. Compound having the formula:

1-propynyl-3,7-dimethyixanthine (1);
1,7-dipropynyl-3-methylxanthine (2);
1-methyl-3,7-dipropynylxanthine (3);
1,3-dipropynyl-7-methylxanthine (4);
1,3,7-tripropynylxanthine (5).

8. Compound having the formula:

1-(4-carboxybutyl)-3,7-dimethylxanthine (22);
1-(3-carboxypropyl)-3,7-dimethyixanthine (23);
1-(3-ethoxycarbonyl)propyl-3,7-dimethylxanthine (24).

9. Compound having the formula:

1,3-dimethyl-7-allyl-8-[(4-trifluoromethyl)fenyl]xanthine (82);
1,3-dimethyl-7-propyl-8-fenylxanthine (112);
1,3,7-tripropyl-8-fenylxanthine (113);
1,7-diallyl-3-propyl-8-fenylxanthine (114);
1,3,7-tripropyl-8-(p-bifenyl)xanthine (116).

10. Compound having the formula:

1,7-diallyl-3-propyl-8-(p-bifenyl)xanthine (117);
1,3,7-tripropyl-8-(4-chlorofenyl)xanthine (118);
1,7-diallyl-3-propyl-8-(4-chlorofenyl)xanthine (119).

11. Use of a compound according to any of the claims 7-10, for the manufacture of a medicament for the treatment of auto-immuno disorders.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 20 1323

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	WO 96 36638 A (CHIROSCIENCE LTD) 21 November 1996 ---		A61K31/52 C07D473/06 C07D473/10
A	EP 0 490 181 A (HOEST-ROUSSEL) 17 June 1992 ---		
A	M.H. HOLSCHBACH ET AL.: "A1 adenosine receptor antagonists as ligands for positron emission tomography and single-photon emission tomography." J. MED. CHAM, vol. 41, no. 4, 1998, pages 555-563, XP002078914 ---		
A	I.A. DOICHINOVA ET AL.: "QSAR studies of 8-substituted xanthines as adenosne receptor antagonists." EUR. J. MED. CHEM., vol. 29, no. 2, 1994, pages 133-138, XP000574700 ---		
A	C.E. MÜLLER ET AL.: "Synthesis of paraxanthine analogs (1,7-disubstituted xanthines) and other xanthines unsubstituted at the 3-position: SAR at adenosine receptor." J. MED. CHEM., vol. 36, no. 22, 1993, pages 3341-3349, XP000574701 ---		TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K C07D
A	M.T. SHAMIN ET AL.: "Effects of 8-phenyl and 8-cyclalkyl substituents on the activity of mono-, di- and trisubstituted alkylxanthnes with substitution at the 1-, 3- and 7-positions." J. MED. CHEM., vol. 32, no. 6, 1989, pages 1231-1237, XP002078917 -----		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 September 1998	Klaver, T

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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